Multiscale Modeling of the Mammalian Circadian Clock: The Role of GABA Signaling

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The mammalian circadian clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus consists of approximately 20,000 pacemaker neurons that are coupled together to produce a robust overall rhythm that drives other bodily functions such as sleep patterns. The SCN represents an ideal model system for studying biological network design and behavior due to accumulating data on individual SCN neurons and their interactions. Experimental studies have shown that SCN intercellular communication is primarily mediated by two neurotransmitters: vasoactive intestinal peptide (VIP) and γ-aminobutyric acid (GABA). While VIP is well established as an essential synchronizing agent, the role of GABA remains controversial. Improved understanding of neurotransmitter mediated intercellular signaling in the SCN will have important clinical implications for prevention and treatment of circadian rhythm disruptions, including mood and sleep disorders and metabolic diseases.

The goal of this project is to develop a multiscale model of the SCN and to integrate this model with targeted experiments and novel computational tools to gain improved understanding of SCN connectivity, synchronization and entrainment properties. The research focuses on GABA signaling because its role in the SCN is prominent, not well understood, and recent advances by the three participating investigators will enable a complete and careful dissection of the role of this common neurotransmitter with synapse-level resolution across large arrays of circadian neurons. The multiscale model will establish a link between core clock genes and ion channels at the individual cell level and network synchronization and entrainment behavior at the SCN tissue level through cell-to-cell connectivity. The research has the potential to be highly transformative by both advancing the multiscale modeling of coupled oscillators/complex networks and by fundamentally changing our understanding of GABA signaling in circadian timekeeping and potentially in other brain regions.

This poster shows the progress during the first 18 months of our project with respect to the development of integrated experimental, modeling and computational methods aimed at unraveling the effects of environmental conditions on the network topology, synchronization behavior and entrainment properties of the SCN. Following our recent publication showing that astrocytes regulate daily rhythms in SCN neurons and in locomotor behavior, we are testing the hypothesis that feedback signals from SCN neurons synchronize daily rhythms in astrocytes. We have found that blocking neuronal firing disrupts synchrony among SCN astrocytes. We are developing a two-color system for simultaneous monitoring of astrocyte-neuron circadian interactions. Motivating by these results and the importance of astrocyte modulation of GABA signaling in the SCN, we have been developing the first mathematical model of SCN astrocytes. The model describes the exchange of GABA and glutamate between single astrocytes and neurons and captures the ability of astrocytes to adjust the neuron period. During the next year, we will be refining our astrocyte model and developing large network models with a sparse network of astrocytes overlaying a dense network of neurons. While working on the detailed biophysical model, we are also developing data driven techniques for (a) its effective reduction (using manifold learning tools like diffusion maps, and equation free approaches, discovering reduced descriptors of the detailed model state) and (b) accelerating its simulation / parametric analysis through this effective reduction using equation-free techniques.